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Intestinal Barriers to Water-Soluble Macromolecules

by James G. Lecce*

Neonates of some species of mammals absorb water-soluble macromolecules from the lumen of the gut to the circulation. This is a means for providing the neonate with passive immunological protection. The accepted model for absorption of macromolecules, particularly immunoglobulin G (IgG), has at least three phases: adherence of the macromolecule to the brush border on enterocytes; internalization of the macromolecule within the enterocytes; and egress of the macromolecule into the lamina propria. With regard to the absorption of IgG, adherence is thought to be a specific reaction of ligand (IgG) with a plasmalemma binding site. Pinocytosis is activated and internalization follows. Egress into the lamina propria occurs at the basal-lateral membrane by a process of reverse pinocytosis. Unbound (unprotected) macromolecules that are internalized in the pinocytosic fluid are shunted off to lysosomes and either digested or stored therein. Neonatal rodents fit this model for macromolecular absorption. However, in another group of neonates (e.g., pig, cow, horse), nonselected absorption takes place, in that IgG and other macromolecules are transported from the gut lumen to the blood. In a third group of neonates, (e.g., human, guinea pig) absorption of IgG is either of low order or nonexistent. Since neonatal mammals possess a mechanism for absorbing macromolecules, there is the potential for internalizing toxic macromolecules if the toxin is presented to the neonate's enterocytes in competitive amounts. Adults retain remnants of the neonatal absorptive mechanism.

The fetus floats in the warm, cosy, protected environment of the uterus — an arrangement of delight. Birth, with all the accompanying trials and traumas, forces the neonate to develop a staggering array of physiological systems independent of his dam. Paramount, the neonate must locate a source of nutrients and at the same time ward off the potential microbial pathogens that are now part of the hostile environment. These two requirements are not necessarily independent. If the neonate attaches to the dam's lactating mammary gland, then the neonate will be provided with a diet that has been honed, through the millenia of mutation and selection, to the neonate's special nutrient needs. In addition, the diet will provide the neonate with immunoglobulins specifically tailored via antibodies to antagonize and neutralize the potential pathogens of the environment. The main thrust of this discussion is devoted to the means whereby the neonate acquires passive protection to pathogens by absorbing immunoglobulins from the dam's colostrum and milk. Inherent in this system for absorbing macromolecules is the potential for absorbing toxic macromolecules.

Absorption of Macromolecules by Neonates

Neonatal mammals can be divided into three groups with regard to when they acquire passive immunity (*1*, *2*). Group I mammals acquire passive immunity from their dam exclusively postpartum; examples are: pig, horse, cow. Group II acquire passive immunity both pre- and postpartum; examples are: mouse, rat, hamster. Group III acquire passive immunity exclusively prepartum; examples are: human, monkey, guinea pig.

Over the years, our research interests have focused on the neonatal pig (group I). The motivation for dealing with this neonate was the desire to resolve the seeming paradox that it was much easier to rear artificially the presumed more fragile human baby than the presumed more hardy pig baby. In redressing this paradox, we designed a successful rearing regimen that uses an automatic feeding de-

*Department of Animal Science and Microbiology, North Carolina State University, Raleigh, North Carolina 27607.

vice that feeds the piglet hourly a liquid diet that is similar to sow's milk — just as the sow feeds her piglet. When pathogens are in the piglet's environment, we must fortify the diet with immunoglobulin, again just as the sow does (*3*).

Why must we provide immunoglobulins in the diet for neonatal pigs but not humans? As mentioned earlier, the human is born with a spectrum of immunoglobulin G antibodies that reflect the immunological history of the mother, and with the pig the risk is run for he is born with little or none. We can, however, rear the pig artificially if care is taken, through sanitation and isolation, to limit the neonates contact with pathogens.

Germane to this discussion, the pig is born void of circulating immunoglobulins, and the sow is secreting large amounts of immunoglobulins. Shortly after nursing, the piglet absorbs into his blood large amounts of the sow's antibodies, intact and unaltered (*4*). The mechanism whereby the immunoglobulin is absorbed has at least three phases; an attachment of immunoglobulin onto the brush border of the intestinal epithelial cell; internalization of the adsorbed immunoglobulin via pinocytosis; and egress or transport of the internalized immunoglobulin into the circulation of the pig (*5, 6*). The pig is nonselective in the uptake and transport of macromolecules. A wide variety of macromolecules, including albumins, dextrans and polyvinlypyrrolidone are absorbed from the lumen of the entire small intestines into the blood (*4*). The phase of transport or egress of the macromolecules into the circulation ceases before the internalization phase (*7*). That is, piglets do not transport macromolecules from their enterocytes to the blood after approximately 2 days of age but continue to internalize macromolecules nonselectively for the next two weeks or so (Fig. 1).

"Closure" is the term applied to the phenomenon of maturation when the intestinal epithelium can no longer internalize macromolecules (*7*). Closure occurs first in the duodenum about 2 days post-partum and proceeds gradually to the ileum ending at about 2 weeks post-partum. This pattern of maturation (cessation of transport at around 2 days of age and the diminishing capacity to internalize over an extended period) is typical for animals that are born with little or no immunoglobulin (Group I).

In group II, animals like neonatal mice and rats

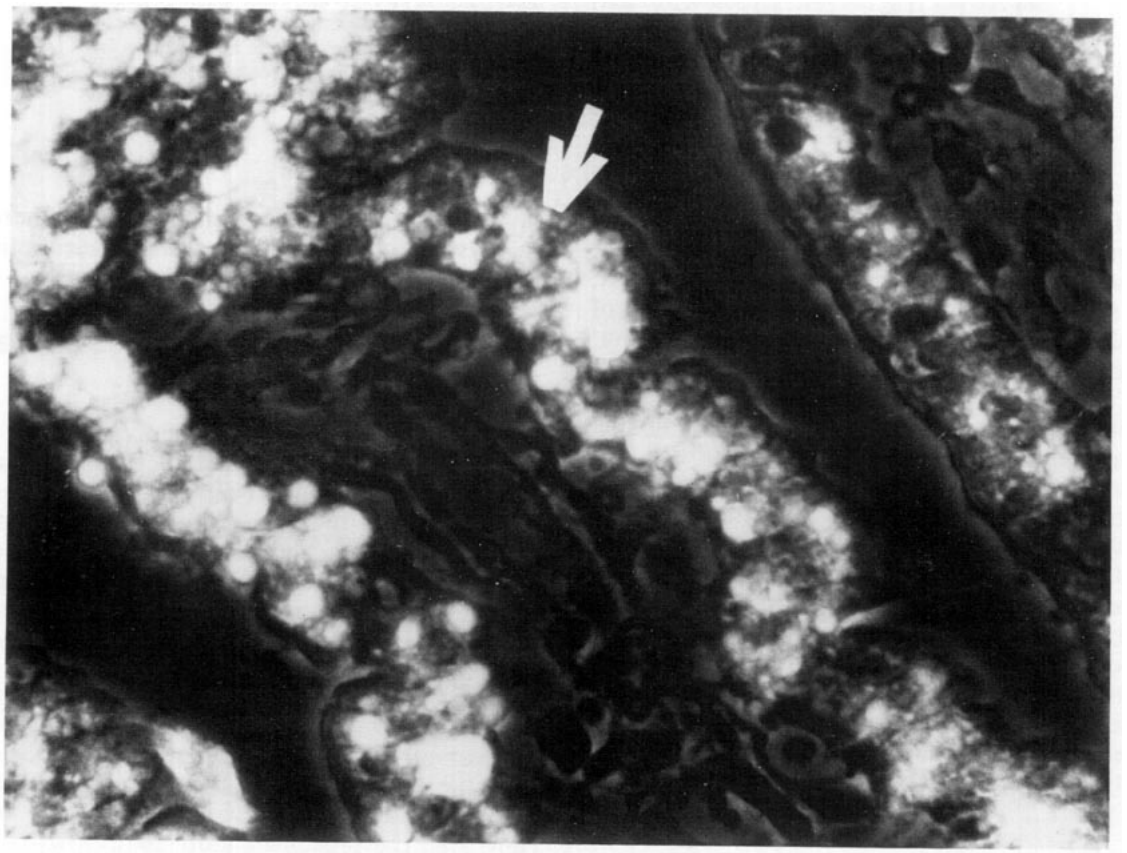

FIGURE 1. Jejunal section from a neonatal pig that was gavaged with fluorescent porcine gamma globulin. Arrow points to fluorescent gamma globulin, internalized within enterocytes, X 450.

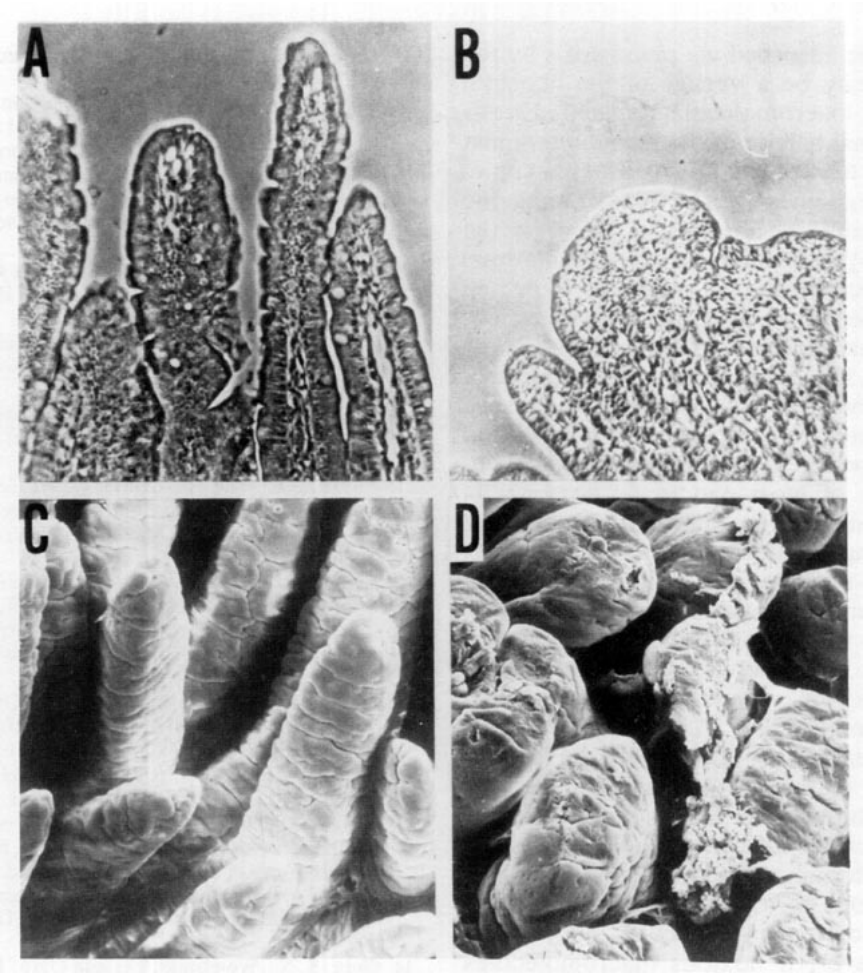

FIGURE 2. Jejunal sections from a neonatal pig: (*A*) Phase contrast photomicrograph of normal villi from an uninfected 2-day-old pig, × 75; (*B*) phase contrast photomicrograph of blunted, shortened, and fused villi from a pig infected with rotavirus at birth and killed 2 days later, × 75; (*C*) Same as *A*, except scanning electronmicrograph, × 413; (*D*) Same as *B*, except scanning electronmicrograph, × 413.

selectively transport only immunoglobulin-G from the gut lumen to the blood. This transport phase is longer for group II animals. That is, mice transport immunoglobulin-G for about 17 days and rats 21 days post-partum. Like the pig, these neonates internalize macromolecules nonselectively (*8*). However, unlike the pig, nonselective internalization occurs from mid-gut to ileum only (*9, 10*). These neonates, again unlike the pig, selectively transport immunoglobulin-G from the upper gut only. Both closure (internalization) and transport cease at the same time (*11*).

Animals in group III, e.g., human infants, have been little studied with regard to the capacity of the neonate's gut to internalize and transport macromolecules. There is morphological evidence from electronmicroscopy of late term fetuses that the intestinal epithelial cell is capable of pinocytosing in bulk quantities (*12, 13*), and serological evidence that the nursing human infant can absorb antibodies from the milk into the blood (*14*). Also foreign antigens have been found in the blood of artificially-fed infants (*15*). The antigens and antibodies formed to these antigens are reflective of the artificial diet. Absorption of macromolecules is difficult to detect and is of a lower order of magnitude than that found in group I and II animals.

Absorption of Macromolecules by Adults

Recent research dealing with the adult rat using highly sensitive techniques such as enzyme markers indicate that trace or antigenic amounts of mac-

romolecules can be adsorbed via pinocytosis by the adult (*15*). This may be a vestige of the neonatal system. Although, macromolecular antigens seem to breach the intestinal barrier in trace amounts, most adults show no ill effect from this natural phenomenon. However, large quantities of toxic or antigenic macromolecules could be absorbed if defects in the host's digestive system were to occur. Abnormal absorption of macromolecules might be expected when there is a decrease in intraluminal digestion, e.g., pancreatic insufficiency, an alteration in intestinal permeability, e.g., a bacterial or viral infection, ulceration, and the like, or a compromise of the host's immune system, e.g., no protective (blocking) antibodies being secreted into the gut lumen. Note, the concentration of most pancreatic enzymes is lower in the neonate than the adult, and the neonate is not yet secreting protective antibodies. Further, we observed that neonatal pigs (with an immature intestinal epithelium) are more susceptible to enteric pathogens such as rotavirus and enterotoxigenic *Escherichia coli* (*16-18*). Rotavirus causes extensive damage to enterocytes, which in turn could affect intestinal permeability (Fig. 2). Immature enterocytes internalize endotoxin (LPS) from the *E. coli*. As the epithelium matures, the piglet becomes less and less vulnerable, both to viruses and bacteria.

In summary, there exists in mammalian neonates a mechanism for internalizing macromolecules. This mechanism functions normally for the absorption of physiologically useful macromolecules, e.g., immunoglobulin. However, if noxious macromolecules are present in competitive amounts in the neonate's environment, then the potential for internalizing a toxic macromolecule exists. A similar situation, but to a lesser extent, may be present in a normal adult and to a greater extent in an adult with a damaged digestive system.

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